



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|   |           |  |
|---|-----------|--|
| <b>(51) International Patent Classification <sup>7</sup> :</b><br><b>C07C 227/40, 229/28</b>  | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 00/01660</b><br><b>(43) International Publication Date:</b> 13 January 2000 (13.01.00)   |
| <b>(21) International Application Number:</b> PCT/EP99/04289<br><b>(22) International Filing Date:</b> 21 June 1999 (21.06.99)<br><br><b>(30) Priority Data:</b><br>MI98A001535      3 July 1998 (03.07.98)      IT<br><br><b>(71) Applicant (for all designated States except US):</b> ZAMBON GROUP S.P.A. [IT/IT]; Via della Chimica, 9, I-36100 Vicenza (IT).<br><br><b>(72) Inventors; and</b><br><b>(75) Inventors/Applicants (for US only):</b> PAIOCCHI, Maurizio [IT/IT]; Via Valsesia, 86/b, I-20152 Milano (IT). ARRIGHI, Katuscia [IT/IT]; Viale Brianza, 17, I-22060 Cabiato (IT). RUSSO, Laura [IT/IT]; Via Lucio Cornelio Silla, 156/c, I-20153 Milano (IT). VILLA, Marco [IT/IT]; Viale Lunigiana, 10, I-20125 Milano (IT).<br><br><b>(74) Agent:</b> LONGONI, Alessandra; Zambon Group S.p.A., Corp. Patent & Trademark Dept., Via Lillo del Duca, 10, I-20091 Bresso (IT). |           | <b>(81) Designated States:</b> CA, CZ, HU, IL, IN, KR, SI, SK, US, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).<br><br><b>Published</b><br><i>With international search report.</i> |
| <b>(54) Title:</b> PROCESS FOR THE PREPARATION OF GABAPENTIN<br><br><b>(57) Abstract</b><br><br>A process for the preparation of pure gabapentin in anhydrous form by treating an aqueous suspension of gabapentin with 2-methoxyethanol or 2-ethoxyethanol and crystallising with an alcoholic solvent is described.   |           |  |

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

|    |                          |    |  |    |  |    |                          |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania                  | ES | Spain                                    | LS | Lesotho                                      | SI | Slovenia                 |
| AM | Armenia                  | FI | Finland                                  | LT | Lithuania                                    | SK | Slovakia                 |
| AT | Austria                  | FR | France                                   | LU | Luxembourg                                   | SN | Senegal                  |
| AU | Australia                | GA | Gabon                                    | LV | Latvia                                       | SZ | Swaziland                |
| AZ | Azerbaijan               | GB | United Kingdom                           | MC | Monaco                                       | TD | Chad                     |
| BA | Bosnia and Herzegovina   | GE | Georgia                                  | MD | Republic of Moldova                          | TG | Togo                     |
| BB | Barbados                 | GH | Ghana                                    | MG | Madagascar                                   | TJ | Tajikistan               |
| BE | Belgium                  | GN | Guinea                                   | MK | The former Yugoslav<br>Republic of Macedonia | TM | Turkmenistan             |
| BF | Burkina Faso             | GR | Greece                                   |    |  | TR | Turkey                   |
| BG | Bulgaria                 | HU | Hungary                                  | ML | Mali   | TT | Trinidad and Tobago      |
| BJ | Benin                    | IE | Ireland                                  | MN | Mongolia                                     | UA | Ukraine                  |
| BR | Brazil                   | IL | Israel                                   | MR | Mauritania                                   | UG | Uganda                   |
| BY | Belarus                  | IS | Iceland                                  | MW | Malawi                                       | US | United States of America |
| CA | Canada                   | IT | Italy                                    | MX | Mexico                                       | UZ | Uzbekistan               |
| CF | Central African Republic | JP | Japan                                    | NE | Niger  | VN | Viet Nam                 |
| CG | Congo                    | KE | Kenya                                    | NL | Netherlands                                  | YU | Yugoslavia               |
| CH | Switzerland              | KG | Kyrgyzstan                               | NO | Norway                                       | ZW | Zimbabwe                 |
| CI | Côte d'Ivoire            | KP | Democratic People's<br>Republic of Korea | NZ | New Zealand                                  |    |                          |
| CM | Cameroon                 | KR | Republic of Korea                        | PL | Poland                                       |    |                          |
| CN | China                    | KZ | Kazakhstan                               | PT | Portugal                                     |    |                          |
| CU | Cuba                     | LC | Saint Lucia                              | RO | Romania                                      |    |                          |
| CZ | Czech Republic           | LI | Liechtenstein                            | RU | Russian Federation                           |    |                          |
| DE | Germany                  | LK | Sri Lanka                                | SD | Sudan  |    |                          |
| DK | Denmark                  | LR | Liberia                                  | SE | Sweden                                       |    |                          |
| EE | Estonia                  |    |  | SG | Singapore                                    |    |                          |

"Process for the preparation of gabapentin"

\*\*\*\*\*

5 The present invention relates to a process for the preparation of gabapentin and, more particularly, it relates to a process for the preparation of gabapentin in anhydrous form by treating an aqueous suspension of gabapentin with 2-methoxyethanol or 2-ethoxyethanol and crystallising with an alcoholic solvent.

10 Gabapentin, 1-(aminomethyl)cyclohexanacetic acid (The Merck Index, XII ed., page 733, no. 4343), is a known drug with anti-epileptic activity described for the first time by Warner-Lambert Co. in the US patent 4,024,175.

15 In the literature several processes for the preparation of gabapentin in anhydrous form are reported (see for example the patents US 4,024,175, US 5,068,413 and US 5,091,567). Substantially all these methods foresee a final step for the purification of gabapentin which consists in the treatment of an aqueous solution of a gabapentin salt (generally hydrochloride) through a weak basic ionic exchange resin, the complete evaporation of water from the aqueous gabapentin solution eluted from the resin and the crystallisation from an alcoholic solvent, generally methanol or methanol/isopropanol mixtures.

20 The complete evaporation of water, described in the above-cited patents, is an expensive and difficult operation with little reproducibility at industrial level, because the product precipitates on the reactor walls and therefore the mixture cannot be stirred. Furthermore, the yield of the subsequent crystallisation depends on the amount of water remained in the product.

25 In the US patent 4,894,476 is underlined that a further problem related to the known methods for the preparation of gabapentin is the amount of residual solvent contained in the product (column 1, lines 56-59). The same patent describes, as a solution of the problem of the residual solvents, a process for the preparation of anhydrous gabapentin on a large scale that uses monohydrate gabapentin as starting material. However, the preparation of monohydrate gabapentin is particularly troublesome because it foresees, after the usual treatment of an aqueous solution of a gabapentin salt through a weak basic ionic exchange resin, the partial evaporation of water from the aqueous gabapentin solution eluted from the resin, the addition of an alcoholic solvent and the crystallisation.

35 The resultant pure monohydrate gabapentin is then dissolved in warm methanol, diluted with isopropanol and crystallised obtaining anhydrous gabapentin with a content of methanol and of isopropanol equal to 100 ppm respectively.

- 2 -

We have now found a method for the preparation of anhydrous gabapentin that allows to obtain the product with a high purity degree and with a low content of residual solvents without using monohydrate gabapentin.

- 5 Therefore, object of the present invention is a process for the preparation of pure gabapentin in anhydrous form comprising (a) the addition of 2-methoxyethanol or of 2-ethoxyethanol to an aqueous gabapentin suspension, (b) the removal of water by azeotropic distillation up to obtain a suspension still containing 20-30% by weight of water with respect to gabapentin, (c) the dilution with an alcoholic solvent and the
- 10 cooling to a temperature from -10°C to +10°C and (d) the filtration and the drying of the crystallised of gabapentin.

The anhydrous gabapentin obtained with the process object of the present invention is characterised by a high purity degree and by a total content of residual solvents lower than 100 ppm.

- 15 Preferably in step (a) of the process 2-methoxyethanol is used.

The amount of 2-methoxyethanol or of 2-ethoxyethanol that is added is not a critical parameter but it will obviously depend on the amount of water present in the aqueous gabapentin suspension to be treated. Generally the aqueous suspension which 2-methoxyethanol or 2-ethoxyethanol is added has a gabapentin

20 concentration from 30% to 40% (w/w). The amount of 2-methoxyethanol or of 2-ethoxyethanol must allow the removal of water by azeotropic distillation up to a residual amount equal to 20%-30% by weight with respect to gabapentin, according to what foreseen in step (b) of the process.

Preferably an amount of 2-methoxyethanol or 2-ethoxyethanol corresponding to 2-5

25 times the amount by weight of gabapentin, still more preferably corresponding to 2-3 times by weight, is used.

In step (b) the gabapentin suspension is heated under reduced pressure by distilling the water/2-methoxyethanol or 2-ethoxyethanol mixture. Preferably a temperature from 40°C to 50°C and a pressure from 50 to 80 mmHg are used.

- 30 In the subsequent step (c), the suspension is diluted with an alcoholic solvent.

The amount of alcoholic solvent is generally from 4 to 10 times by weight with respect to gabapentin, preferably from 4 to 6 times by weight.

Examples of alcoholic solvents are linear or branched C<sub>1</sub>-C<sub>4</sub> alcohols such as methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol, isobutanol, *sec*-butanol, *tert*-

35 butanol and mixtures thereof.

Isopropanol is preferably used.

- 3 -

After optional heating to a temperature from 50°C to 70°C, the mixture is cooled to a temperature from -10°C to +10°C, preferably from -5°C to 0°C.

5 The subsequent step (d) foresees the filtration and the drying of the crystallised according to conventional techniques so allowing to obtain gabapentin in pure anhydrous form (HPLC titre > 99.5%) and with a content of residual solvents (alcoholic solvent + 2-methoxyethanol or 2-ethoxyethanol) lower than 100 ppm.

10 The aqueous gabapentin suspension used as starting product in the process object of the present invention is generally an aqueous suspension obtained after elution from a weak basic ionic exchange resin, according to one of the methods described in the literature, and concentration.

15 Preferably the aqueous gabapentin suspension used as starting product comes from the elution of a gabapentin hydrochloride solution through a Relite EXA10 resin. The aqueous solution obtained after crossing through this resin results to be much more concentrated with respect to those obtained after crossing through the resins described in the literature, giving a significant industrial advantage.

20 Therefore a further object of the present invention is a process for the preparation of pure gabapentin in anhydrous form comprising the preparation of an aqueous gabapentin solution by eluting a gabapentin salt solution through a Relite EXA10 resin, the concentration up to obtain an aqueous gabapentin suspension at 30%-40% by weight and the subsequent treatment according to what foreseen in the already reported steps (a), (b), (c) and (d).

Gabapentin hydrochloride can be prepared according to one of the methods described in the literature.

25 The process object of the present invention has the advantage to avoid the complete removal of water and to be reproducible at industrial level because, during the concentration phase, the mass can be always easily stirred. The used amount of solvent is reduced (high productivity) and the product is obtained in anhydrous form with yields higher than 90%, even in the presence of amounts of water higher than 30% w/w with respect to gabapentin.

The content of residual solvents is extremely low, generally lower than 100 ppm, notwithstanding gabapentin monohydrate is not used.

In order to better illustrate the present invention the following examples are now given.

35

## Example 1

- 4 -

Water (130 g), gabapentin hydrochloride (40 g; HPLC titre 94%), prepared according to the process described in US 4,024,175, and charcoal L4S (1.0 g) were charged into a 250 ml reactor at room temperature.

- 5 After keeping under stirring for 15 minutes, the mixture was filtered through a celite panel and the panel was washed with water (5 g). The solution was pumped with a flux of 15 ml/minute in a column containing Relite EXA10 resin (115 ml). At the end of the addition of the solution, the elution of water in the column went on and the solution was collected following the BRIX index.
- 10 The resultant aqueous gabapentin solution (300 g; HPLC titre 10.06%) was concentrated under vacuum (25 mmHg/50°C) up to obtain a stirrable mixture (still containing 46 g of water).  
2-Methoxyethanol (80 ml) was added and a water/2-methoxyethanol mixture (50:50 w/w; 76 g) was distilled under vacuum (40-45°C/60 mmHg).
- 15 Isopropanol (180 ml) was added to the suspension and the mixture was heated at 60°C for 30 minutes.  
After cooling at 20°C in about 2 hours, the mixture was kept 2 hours at -5°C/-10°C.  
The precipitate was filtered and washed with isopropanol (2x10 ml).  
After drying under vacuum at 50°C up to constant weight pure gabapentin (28.3 g)
- 20 was obtained.  
HPLC titre=99.8%; K.F.=0.05%  
Isopropanol < 30 ppm  
2-methoxyethanol < 70 ppm.

#### Example 2

- 25 2-Methoxyethanol (200 ml) and gabapentin hydrochloride (100 g; HPLC titre 92%) were charged into a 0.5 l reactor, equipped with mechanic stirring, condenser and thermometer, kept under inert atmosphere.  
The suspension was heated at internal 50-55°C for 30 minutes. The insoluble (about 4 g) was filtered and the solution was concentrated under vacuum (external 50°C; 30 mmHg) distilling about 115 g of 2-methoxyethanol. Water (250 ml) was added to the residue, kept warm.
- 30 The mixture was kept under stirring up to obtain a solution.  
The solution, cooled and kept at room temperature, was pumped with a flux of 15 ml/minute into a column containing Relite EXA10 resin (300 ml).
- 35 At the end of the addition of the solution, the elution of water in the column went on and the solution was collected following the BRIX index.

- 5 -

The resultant aqueous gabapentin solution (580 g; HPLC titre 12.7%) was heated at 45°C and then charcoal L4S (5 g) was added.

- 5 The mixture was kept under stirring for 30 minutes and filtered through a celite panel that was washed with water (15 ml).

The aqueous solution was concentrated under vacuum (25 mmHg/50-55°C) up to obtain a stirrable mixture (weight of the distilled about 380 g). 2-Methoxyethanol (180 ml) was added and the mixture was concentrated at an internal temperature of 40°C at 60 mmHg (distilled about 180 ml of water/2-methoxyethanol=1/1).

10. Isopropanol (400 ml) was added to the suspension and, after heating at 60°C, the mixture was kept at that temperature for 30-60 minutes and then was cooled in about 2 hours at 20°C and then at -5°C.

After 2 hours at -5°C, the precipitate was filtered, washed with isopropanol (2x25 ml) and dried under vacuum at 50°C up to constant weight obtaining pure gabapentin

- 15 (68 g). HPLC titre=100%; K.F.=0.05%  
residual solvent (isopropanol + 2-methoxyethanol) < 100 ppm

- 6 -

Claims

- 1) A process for the preparation of pure gabapentin in anhydrous form comprising  
(a) the addition of 2-methoxyethanol or of 2-ethoxyethanol to an aqueous  
gabapentin suspension, (b) the removal of water by azeotropic distillation up to  
obtain a suspension still containing 20-30% by weight of water with respect to  
gabapentin, (c) the dilution with an alcoholic solvent and the cooling to a  
temperature from -10°C to +10°C and (d) the filtration and the drying of the  
crystallised of gabapentin.
- 2) A process according to claim 1 wherein 2-methoxyethanol is used.
- 3) A process according to claim 1 wherein an amount of 2-methoxyethanol or 2-  
ethoxyethanol corresponding to 2-5 times the amount by weight of gabapentin is  
used.
- 4) A process according to claim 3 wherein the amount corresponds to 2-3 times by  
weight.
- 5) A process according to claim 1 wherein step (b) is carried out at a temperature  
from 40°C to 50°C and at a pressure from 50 to 80 mmHg.
- 6) A process according to claim 1 wherein the alcoholic solvent is a linear or  
branched C<sub>1</sub>-C<sub>4</sub> alcohol selected among methanol, ethanol, *n*-propanol,  
isopropanol, *n*-butanol, isobutanol, *sec*-butanol, *tert*-butanol and mixtures  
thereof.
- 7) A process according to claim 1 wherein the amount of alcoholic solvent is from 4  
to 10 times by weight with respect to gabapentin.
- 8) A process according to claim 7 wherein the amount is from 4 to 6 times by  
weight.
- 9) A process according to claim 6 wherein the solvent is isopropanol.
- 10) A process according to claim 1 wherein, in step (c), the mixture is cooled at a  
temperature from -5°C to 0°C.
- 11) A process according to claim 1 further comprising the preparation of an aqueous  
gabapentin solution by elution of a gabapentin salt solution through a Relite  
EXA10 resin, the concentration up to obtain an aqueous gabapentin suspension  
at 30%-40% by weight.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/04289

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C227/40 C07C229/28

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                   | Relevant to claim No. |
|------------|--|-----------------------|
| A          | US 4 894 476 A (DONALD E. BUTLER ET AL.)<br>16 January 1990 (1990-01-16)<br>cited in the application<br>examples 2,3 | 1                     |
| A          | US 4 024 175 A (GERHARD SATZINGER ET AL.)<br>17 May 1977 (1977-05-17)<br>cited in the application<br>example 1       | 1                     |
| A          | US 5 068 413 A (KLAUS STEINER ET AL.)<br>26 November 1991 (1991-11-26)<br>cited in the application<br>examples 3,6   | 1                     |

☐ Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

6 October 1999

Date of mailing of the international search report

19/10/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Zervas, B

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/04289

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| US 4894476 A                              | 16-01-1990          | AT 101116 T                | 15-02-1994          |
|   |                     | AU 624130 B                | 04-06-1992          |
|   |                     | AU 3267889 A               | 02-11-1989          |
|   |                     | CA 1306755 A               | 25-08-1992          |
|   |                     | DE 68912819 D              | 17-03-1994          |
|   |                     | DE 68912819 T              | 19-05-1994          |
|   |                     | DK 212689 A                | 03-11-1989          |
|   |                     | EP 0340677 A               | 08-11-1989          |
|   |                     | ES 2061774 T               | 16-12-1994          |
|   |                     | FI 892067 A                | 03-11-1989          |
|   |                     | HK 1000798 A               | 01-05-1998          |
|   |                     | IE 62958 B                 | 08-03-1995          |
|   |                     | JP 2011546 A               | 16-01-1990          |
|   |                     | JP 2619951 B               | 11-06-1997          |
|   |                     | US 4960931 A               | 02-10-1990          |
| US 4024175 A                              | 17-05-1977          | DE 2460891 A               | 01-07-1976          |
|   |                     | AT 340892 B                | 10-01-1978          |
|   |                     | AT 975075 A                | 15-05-1977          |
|   |                     | AU 8774175 A               | 23-06-1977          |
|   |                     | BE 836835 A                | 18-06-1976          |
|   |                     | CA 1052811 A               | 17-04-1979          |
|   |                     | CH 612665 A                | 15-08-1979          |
|   |                     | CH 612666 A                | 15-08-1979          |
|   |                     | CH 612664 A                | 15-08-1979          |
|   |                     | DE 2543821 A               | 14-04-1977          |
|   |                     | DK 581475 A,B,             | 22-01-1976          |
|   |                     | ES 443723 A                | 16-04-1977          |
|   |                     | FI 753613 A,B,             | 22-06-1976          |
|   |                     | FR 2294697 A               | 16-07-1976          |
|   |                     | GB 1465229 A               | 23-02-1977          |
|   |                     | IE 42382 B                 | 30-07-1980          |
|   |                     | JP 941538 C                | 20-02-1979          |
|   |                     | JP 51088940 A              | 04-08-1976          |
|   |                     | JP 53024064 B              | 18-07-1978          |
|   |                     | LU 74058 A                 | 20-07-1976          |
|   |                     | NL 7514900 A,B,            | 23-06-1976          |
|   |                     | SE 423385 B                | 03-05-1982          |
|   |                     | SE 7514442 A               | 22-06-1976          |
|   |                     | US 4087544 A               | 02-05-1978          |
| US 5068413 A                              | 26-11-1991          | DE 3928184 A               | 28-02-1991          |
|   |                     | AT 98219 T                 | 15-12-1993          |
|   |                     | DE 59003771 D              | 20-01-1994          |
|   |                     | DK 414275 T                | 14-02-1994          |
|   |                     | EP 0414275 A               | 27-02-1991          |
|   |                     | ES 2059938 T               | 16-11-1994          |
|   |                     | FI 103506 B                | 15-07-1999          |
|   |                     | IE 63922 B                 | 14-06-1995          |
|   |                     | IL 95480 A                 | 29-06-1995          |
|   |                     | JP 2839344 B               | 16-12-1998          |
|   |                     | JP 3090054 A               | 16-04-1991          |
|   |                     | PT 95099 A,B               | 18-04-1991          |